# External Validation of a Risk Model to Predict Recurrence-Free Survival After Radical Cystectomy in Patients With Pathological Tumor Stage T3N0 Urothelial Carcinoma of the Bladder

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**Abbreviations and Acronyms**

c-index = concordance index
CSS = carcinoma specific survival
RC = radical cystectomy
RFS = recurrence-free survival
LVI = lymphovascular invasion
PSM = positive surgical margin
UCB = bladder urothelial carcinoma

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**Purpose:** Patients with stage pT3N0 urothelial bladder cancer vary in outcome after radical cystectomy. To improve prognosis estimation a model was recently developed that defines 3 risk groups for recurrence-free survival based on pT substaging, lymphovascular invasion and positive surgical margin. We present what is to our knowledge the first external validation of this risk model.
**Materials and Methods:** Analogous to the risk model derivation cohort our study group comprised 472 patients with stage pT3, pN0, cM0 disease without perioperative chemotherapy and with a median followup of 42 months (IQR 20–75). The primary end point was recurrence-free survival. The effect of variables was determined by univariate and multivariate Cox regression analysis, and predictive accuracy was determined by ROC analysis.
**Results:** Stage pT3aN0 and pT3bN0 cases showed significantly different recurrence-free survival after 5 years (51% vs 29%, $p < 0.001$). In the multivariate Cox model pT3 substage (HR 1.86, $p < 0.001$), lymphovascular invasion (HR 1.48, $p = 0.002$), positive surgical margins (HR 1.90, $p = 0.030$) and patient age with a dichotomy at 70 years (HR 1.51, $p = 0.001$) had an independent effect on recurrence-free survival. In the low (221 patients or 47%), intermediate (184 or 39%) and high (67 or 14%) risk groups the 5-year recurrence-free survival rate was 55%, 45% and 13%, respectively ($p < 0.001$). The concordance index of the risk model to predict recurrence-free survival was 0.64 (95% CI 0.59–0.69).
**Conclusions:** This user friendly risk model can be recommended to estimate prognosis in patients with stage pT3N0 after radical cystectomy. Patients at high risk showed clearly compromised recurrence-free survival and should be included in adjuvant therapy studies.

**Key Words:** urinary bladder, urothelium, carcinoma, mortality, Germany

Patients with stage T3N0 UCB are substratified (pT3aN0 vs pT3bN0) by the extent of tumor infiltration into perivesical fat.[1] This subdivision had prognostic relevance in 1 outcome study of RC[2] while other studies showed no difference in survival.[3–5] Clinical studies seeking to establish


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the value of adjuvant chemotherapy regularly include data on patients with pT3N0, although these patients often show large variance in disease progression after RC.[1,6,7] Individual prognostic estimations for these patients using the 2 currently accepted outcome nomograms, which were developed by analyzing a heterogeneous patient group, do not consider pT3 substage or the specific influence of other prognostic parameters.[8,9] Other than stratification based on pT3 substage and available nomograms, more accurate survival prediction and enhanced classification of patients with a compromised prognosis would enable us to include them in adjuvant therapy studies.

Sonpavde et al recently developed a risk model based on substaging pT3, LVI and PSM that permits the subdivision of stage pT3N0 UCB cases without perioperative chemotherapy into 3 groups with a significant difference in RFS.[10] This user friendly risk model should be externally validated before its implementation in clinical decision making.

In this German multicenter RC series we performed targeted analysis of the oncological course of patients with pT3N0 UCB without perioperative chemotherapy as well as what is to our knowledge the first external validation of the risk model of Sonpavde et al.[10]

## MATERIALS AND METHODS

After receiving approval from the local ethics commissions clinical and pathological data on 2,556 consecutive patients with UCB treated with RC at 6 university health centers and 2 maximum care hospitals from 1989 to 2009 were collated in 1 database. RC indication was based on guidelines in place at the time of the procedure. The 55 patients with neoadjuvant systemic chemotherapy, the 18 with confirmed distant metastasis on preoperative computerized tomography and the 1,965 who did not present with pathological tumor stage T3N0 were stepwise excluded from analysis. Of the remaining 518 patients 46 with adjuvant chemotherapy were excluded from study, resulting in a study group of 472 patients with stage pT3, pN0, cM0 disease without perioperative chemotherapy.

Median followup of survivors at the study end point was 42 months (IQR 20–75). Preoperative staging extent, RC technical aspects, including bilateral extended lymph node dissection with the common ileac nodes, histopathological assessment of RC specimens and followup type, were defined according to standardized internal clinic protocols. The subdivision of infiltration into perivesical fat, as listed in the TNM classification, 5th edition, formed the basis for all histopathological reports.[11]

The pT classification was adapted by the reference pathologist at the respective institution for RC before 1997 (tumor stage pT3b in the TNM classification, 4th edition). pT3 substaging was based on the extent of tumor infiltration in perivesical fat, exclusively microscopically vs macroscopically.[1,11] Tumors were graded according to the 1973 WHO classification.[12] LVI was defined as tumor cells in an endothelial lined space and PSM was defined as tumor cells at the color stained edge of the RC specimen. Analogous to the study by Sonpavde et al, the ureters and the urethra were not considered.[10] All carcinoma in situ associated with the pT3 tumor was recorded. The risk model of Sonpavde et al assigns a score of 0 to 3 points and is calculated by 3 criteria, including pT3 substage (pT3b equals 1 point), LVI (LVI presence equals 1 point) and surgical margins (PSM equals 1 point). Results define 3 risk groups, including 0 points—low, 1—intermediate and 2 or 3—high.

Normally and not normally distributed continuous variables are shown as the mean ± SD or as the median and IQR. Group differences were analyzed by the Student t or the Mann-Whitney Wilcoxon rank sum test. Categorical variables were compared with the chi-square test. RFS and CSS were calculated using the Kaplan-Meier method with group differences assessed by the log rank test.

The influence of various factors on RFS and CSS were investigated using univariate and multivariate Cox proportional hazard regression models with backward stepwise elimination of nonsignificant variables. Analogous to the specifications defined by Sonpavde et al,[10] RFS was defined as the time between RC and recurrence or death independent of cause (primary study end point). Death from an unrelated cause was treated as a censoring event when calculating CSS from the time of death. The c-index was calculated for all investigated variables and for the whole model on ROC analysis. All statistical tests were 2 sided and performed with SPSS®, version 17.0. Results were considered significant at $p \leq 0.05$.

## RESULTS

Patients with stage T3bN0 had undifferentiated carcinoma ($p < 0.001$), LVI ($p = 0.026$), PSM ($p < 0.001$) and associated carcinoma in situ ($p = 0.09$) significantly more often than those with pT3aN0. Applying the risk groups defined by Sonpavde et al[10] resulted in subdivision of the study group, including 221 patients (46.8%) at low risk (score sum 0), 184 (39.0%) at intermediate risk (score sum 1) and 67 (14.2%) at high risk (score sum 2 or 3).

RFS of the study group at 2, 5 and 10 years was 62%, 45% and 31%, respectively. Patients with stages pT3aN0 and pT3bN0 showed a significant difference in 5-year RFS (51% vs 29%, $p = 0.001$). In the multivariate Cox model for RFS pT3 substage (HR 1.86, $p < 0.001$), LVI (HR 1.48, $p = 0.002$), PSM (HR 1.90, $p = 0.030$) and patient age with dichotomization at 70 years (HR 1.51, $p = 0.001$) had an independent effect on RFS.

Patient age was dichotomized at 70 years since this limit provided the largest independent effect from the Cox model. The risk score of Sonpavde et al, consisting of pT3 substage, LVI and PSM, had a c-index of 0.637 (95% CI 0.59–0.69) to predict RFS.[10] Adding age to this score increased the c-in-